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PRRT2-related phenotypes in patients with a 16p11.2 deletion

Danique R.M. Vlaskamp[a,b], Petra M.C. Callenbach[a,1], Patrick Rump[b,1], Lucia A.A. Giannini[b], Eva H. Brilstra[c], Trijnie Dijkhuizen[b], Yvonne J. Vos[b], Anne-Marie F. van der Kevie-Kersemaekers[d], Jeroen Knijnenburg[e], Nicole de Leeuw[f], Rick van Minkelen[e], Claudia A.L. Ruivenkamp[g], Alexander P.A. Stegmann[h], Oebele F. Brouwer[a], Conny M.A. van Ravenswaaij-Arts[b,*]

[a] University of Groningen, University Medical Center Groningen, Department of Neurology, Groningen, The Netherlands
[b] University of Groningen, University Medical Center Groningen, Department of Genetics, Groningen, The Netherlands
[c] University Medical Center Utrecht, Department of Genetics, Utrecht, The Netherlands
[d] Academic Medical Center, Department of Genetics, Amsterdam, The Netherlands
[e] Erasmus Medical Center, Department of Genetics, Rotterdam, The Netherlands
[f] Radboud University Medical Center, Department of Genetics, Nijmegen, The Netherlands
[g] Leiden University Medical Center, Department of Genetics, Leiden, The Netherlands
[h] Maastricht University Medical Center, Department of Genetics, Maastricht, The Netherlands

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ABSTRACT

We studied the presence of benign infantile epilepsy (BIE), paroxysmal kinesigenic dyskinesia (PKD), and PKD with infantile convulsions (PKD/IC) in patients with a 16p11.2 deletion including *PRRT2* or with a *PRRT2* loss-of-function sequence variant. Index patients were recruited from seven Dutch university hospitals. The presence of BIE, PKD and PKD/IC was retrospectively evaluated using questionnaires and medical records. We included 33 patients with a 16p11.2 deletion: three (9%) had BIE, none had PKD or PKD/IC. Twelve patients had a *PRRT2* sequence variant: BIE was present in four ($p = 0.069$), PKD in six ($p < 0.001$) and PKD/IC in two ($p = 0.067$). Most patients with a deletion had undergone genetic testing because of developmental problems (87%), whereas all patients with a sequence variant were tested because of a movement disorder (55%) or epilepsy (45%). BIE, PKD and PKD/IC clearly showed incomplete penetrance in patients with 16p11.2 deletions, but were found in all and 95% of patients with a *PRRT2* sequence variant in our study and a large literature cohort, respectively. Deletions and sequence variants have the same underlying loss-of-function disease mechanism. Thus, differences in ascertainment have led to overestimating the frequency of BIE, PKD and PKD/IC in patients with a *PRRT2* sequence variant. This has important implications for counseling if genome-wide sequencing shows such variants in patients not presenting the *PRRT2*-related phenotypes.

1. Introduction

PRRT2 (MIM 614386) has been identified as a causal gene for benign infantile epilepsy (BIE), paroxysmal kinesigenic dyskinesia (PKD), and paroxysmal kinesigenic dyskinesia with infantile convulsions (PKD/IC) (Chen et al., 2011; Heron et al., 2012; Lee et al., 2012). These clinical entities reflect the core of the *PRRT2*-related phenotypic spectrum (Ebrahimi-Fakhari et al., 2015). Other epilepsies, movement disorders and (hemiplegic) migraine have been reported to be possibly related to *PRRT2* sequence variants (Ebrahimi-Fakhari et al., 2015).

PRRT2 encodes for proline-rich transmembrane protein 2 that interacts with SNAP25 in glutamatergic synapses in the brain to modulate glutamate release (Chen et al., 2011; Heron et al., 2012; Lee et al., 2012; Li et al., 2015). *PRRT2* sequence variants have been shown to result in a loss-of-function of PRRT2, impaired SNAP25 interaction, raised intracellular glutamate levels and increased neuronal hyperexcitability (Lee et al., 2012; Li et al., 2015).

Chromosome 16p11.2 deletions including *PRRT2* are associated with the 16p11.2 microdeletion syndrome (MIM 611913). We expected that 16p11.2 deletions are also associated with *PRRT2*-related phenotypes, because deletions and sequence variants of *PRRT2* share an underlying loss-of-function disease mechanism. So far, only six cases with a 16p11.2 deletion and PKD (n = 4) or PKD/IC (n = 2) have been reported (Lipton and Rivkin, 2009; Dale et al., 2011, 2012; Silveira-

* Corresponding author. Department of Genetics CB50, University Medical Center Groningen, P.O. Box 30.001, 9700 RB, Groningen, The Netherlands.
E-mail address: c.m.a.van.ravenswaaij@umcg.nl (C.M.A. van Ravenswaaij-Arts).
[1] Both authors contributed equally to this work.

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Moriyama et al., 2013; Weber et al., 2013; Termsarasab et al., 2014). Previous large 16p11.2 deletion cohort studies reported seizures in 24–31% of patients, dystonia in 1% and paroxysmal dyskinesia in 5% without classifying these phenotypes as BIE, PKD or PKD/IC (Shinawi et al., 2010; Steinman et al., 2016; Zufferey et al., 2012).

We systematically evaluated the presence of the *PRRT2*-related phenotypes BIE, PKD, and PKD/IC in patients with a 16p11.2 deletion including *PRRT2*, and compared these frequencies with those seen in patients with a *PRRT2* sequence variant.

2. Methods

We identified 129 Dutch-speaking patients with a 16p11.2 deletion including *PRRT2* in seven Dutch university medical centers (UMCs). Five patients were not approached for participation (two were deceased, two had an additional disease-associated 22q11.2 deletion, and one was lost to follow-up before this study). Forty of 124 (32%) patients agreed to participate, including 33/40 (83%) index patients from 33 families.

Following the same strategy, we identified 43 patients with a *PRRT2* sequence variant in three UMCs. One patient was involved in another study and not contacted. Fifteen (36%) patients agreed to participate, including 12/15 (80%) index patients from 12 families.

All patients or their parents/caregivers gave written consent for participation and completed a questionnaire containing (1) a PKD Screening questionnaire, (2) a Headache-Attributed Restriction, Disability, Social Handicap and Impaired Participation questionnaire and (3) questions on epilepsy (seizure onset, remission, frequency and semiology), school performance and development, height, weight and family history (Steiner et al., 2014; Tan et al., 2014). An English version of the questionnaire is available on request.

Phenotypes were compared between index patients with a 16p11.2 deletion (n = 33) and those with a *PRRT2* sequence variant (n = 12). To increase the validity of any observed differences, we compared the phenotypes of patients with a 16p11.2 deletion in our cohort (n = 33) with those of patients with a heterozygous *PRRT2* sequence variant reported in the large review cohort of Ebrahimi-Fakhari (n = 1423, excluding patients with bi-allelic *PRRT2* sequence variants (n = 15) or a 16p11.2 deletion (n = 6)) (Ebrahimi-Fakhari et al., 2015).

Additional information on methods is given in the Supplementary Methods.

3. Results

We included 33 index patients with the recurrent ~600 kb BP4-BP5 16p11.2 deletion (Supplementary Figure 1) and 12 index patients with a disease-associated *PRRT2* sequence variant: c.649dupC; p.(Arg217Profs*8) (n = 10), c.629dupC; p.(Ala211Serfs*14) (n = 1), or c.824C > T; p.(Ser275*) (n = 1) (NM_145239.2, Supplementary Table 1). All variants were added to public databases (see Supplementary methods for more information). Patients with a 16p11.2 deletion most often underwent genetic testing because of developmental delay (87%), while those with a *PRRT2* sequence variant were tested because of a movement disorder (55%) or epilepsy (45%) (Table 1).

Patients with a 16p11.2 deletion less often had a *PRRT2*-related phenotype than those with a *PRRT2* sequence variant (9% *vs.* 100%, $p < 0.001$) (Table 1). These phenotypes concerned BIE (9% *vs.* 33%, $p = 0.069$), PKD (0% *vs.* 50%, $p < 0.001$) and PKD/IC (0% *vs.* 17%, $p = 0.067$) (See Tables 2 and 3 for epilepsy and movement disorder phenotypes, respectively). Comparisons between patients with a 16p11.2 deletion in our cohort and those with a *PRRT2* sequence variant from the review cohort showed significant differences for all *PRRT2*-related phenotypes (Table 1). The presence of other epilepsies, movement disorders, hemiplegic migraine and migraine as possible *PRRT2*-related phenotypes did not significantly differ between the three groups (Tables 1–3, see Supplementary Table 2 for migraine phenotypes).

4. Discussion

We found that only a minority of patients with a 16p11.2 deletion in our cohort suffered from BIE (9%) while none had PKD or PKD/IC. In comparison, patients with a *PRRT2* sequence variant in our cohort (100%) and a review cohort (95%) had these *PRRT2*-related phenotypes significantly more often (Ebrahimi-Fakhari et al., 2015).

It is unlikely that phenotypic differences between the two different genotype cohorts are due to differences in the underlying *PRRT2* disease mechanism. First, *PRRT2*-related phenotypes occurred in both genotype groups in our study and other studies (Lipton and Rivkin, 2009; Dale et al., 2011, 2012; Silveira-Moriyama et al., 2013; Weber et al., 2013; Termsarasab et al., 2014). Second, both genotypes cause a loss-of-function of PRRT2. The p.(Arg217Profs*8) variant, found in most patients of our (83%) and the review (79%) cohort, results in a PRRT2 loss-of-function without a dominant-negative effect (Ebrahimi-Fakhari et al., 2015; Lee et al., 2012; Li et al., 2015). Patients with 16p11.2 deletions have a 50% reduced expression of *PRRT2* and other genes within the deletion region that probably explains their additional problems (Blumenthal et al., 2014). In theory, the deletion of these other genes might have had a protective effect on the patients' phenotypes, but no clear evidence for this hypothesis exists so far.

It seems most likely that differences in ascertaining patients underlie the differences in *PRRT2*-related phenotypes observed in patients with a 16p11.2 deletion versus a *PRRT2* sequence variant. The frequency of phenotypes has probably been overestimated in patients with a *PRRT2* variant, who most often underwent genetic testing because of a movement disorder or epilepsy. The high frequency of the recurrent c.649dupC; p.(Arg217fs) *PRRT2* variant in individuals included in the ExAC Database (1.3%, n = 401/32,017; Exac version 0.3.1) seems to support this hypothesis although the frequency in the gnomAD Database is substantially lower (0.05%, n = 8/14,859; gnomAD version r2.0.2) (Lek et al., 2016). This difference might be related to the used data (whole exome versus whole genome data) or whether DNA amplification was performed, as previously suggested by the relatively high frequency of this variant in the Exome Variant Server database that uses amplification (Huguet et al., 2014). A compatible influence of ascertainment might be present in the published review cohort. The inclusion of index cases in calculating penetrance of *PRRT2* in other studies has probably resulted in an overestimated disease penetrance for PKD (60%) and BIE (60–90%) (Callenbach et al., 2005; Van Vliet et al., 2012). A lower penetrance (48%) has been found in a single family with 23 relatives with *PRRT2* sequence variants (Family 1, excluding the index patient) (Callenbach et al., 2005; De Vries et al., 2012). Reduced penetrance is also known for other clinical features associated with the 16p11.2 BP4-BP5 deletion (Shinawi et al., 2010; Steinman et al., 2016; Zufferey et al., 2012).

The low frequency of *PRRT2*-related phenotypes in our patients with 16p11.2 deletions is in line with two large previous studies showing the presence of any seizures in 24% (n = 49/195) and 27% (n = 22/83), paroxysmal dyskinesia in 5% (n = 12/233) and dystonia in 1% (n = 1/83), emphasizing the incomplete penetrance of BIE and PKD (Shinawi et al., 2010; Steinman et al., 2016; Zufferey et al., 2012). However, in our small cohort, we might have underestimated the presence of *PRRT2*-related phenotypes. First, BIE occurred long time ago in some patients, leading to recall bias, and may have a low seizure-frequency, leading to missed diagnoses. Second, three patients had unwitnessed incidents, but these occurred too late for a diagnosis of BIE. Last, some patients were too young to fully exclude PKD. It is thus possible that the differences in frequencies between the two patient groups might be partly explained by under-recognition of *PRRT2*-related phenotypes in the 16p11.2 microdeletion patients.

The observation that the frequency of *PRRT2*-related phenotypes

Table 1
Phenotypes of patients with a 16p11.2 deletion or a *PRRT2* sequence variant in our cohort and the literature.

	Patients with a 16p11.2 deletion (n = 33)	Patients with a *PRRT2* sequence variant (n = 12)	p-value [a]	Patients with a *PRRT2* sequence variant from the review cohort (n = 1423) [b]	p-value [c]
Patient characteristics at inclusion in study					
Male (%)	19 (57.6)	4 (33)	0.189	NA	NA
Median age in years (range)	12.4 (3.8–37.1)	21.5 (4.5–48.7)	**0.023**	NA	NA
***PRRT2*-related phenotypes**					
Diagnosis in BIE – PKD – PKD/IC spectrum (%)	3 (9.1)	12 (100)	< **0.001**	1352 (95.0)	< **0.001**
BIE (%)	3 (9.1)	4 (33.3)	0.069	598 (42.0)	< **0.001**
PKD (%)	0 (−)	6 (50.0)	< **0.001**	553 (38.9)	< **0.001**
PKD/IC (%)	0 (−)	2 (16.7)	0.067	201 (14.1)	**0.010**
Possible *PRRT2*-related phenotypes					
Other epilepsy diagnosis (%)	2 (6.1)	1 (8.3)	1.000	51 (3.6) [d]	0.340
Other movement disorder diagnosis (%)	1 (3.0)	0 (−)	1.000	19 (1.3) [e]	0.370
Hemiplegic migraine (%)	1/31 (3.2)	3 (25.0)	0.059	34 (2.4)	0.534
Migraine or probable migraine (%)	4/31 (12.9)	1 (8.3)	1.000	68 (4.8)	0.063
16p11.2 deletion-related phenotypes					
Developmental problems (%)	33 (100)	1 (8.3)	< **0.001**	NA	NA
Special education in those > 4 years (%)	29/32 (90.6)	0/11 (−)	< **0.001**	20 (1.4) [f]	< **0.001**
Problems in motor developmental (%)	28 (84.8)	1 (8.3)	< **0.001**	NA	NA
Problems in language development (%)	32 (97.0)	0 (−)	< **0.001**	NA	NA
Median age in months at					
sitting (range, known in n)	10.0 (6.0–48.0, 28)	9.0 (7.0–11.0, 7)	0.340	NA	NA
walking (range, known in n)	19.8 (12.0–30.0, 30) [g]	14.5 (11.0–22.0, 8)	< **0.001**	NA	NA
speaking first word (range, known in)	17.5 (9.0–84.0, 24) [g]	11.5 (9.0–12.0, 6)	**0.003**	NA	NA
speaking comprehensively (range, known in n)	48.0 (18.0–72.0, 15) [g]	18.0 (16.0–30.0, 6)	**0.001**	NA	NA
Obesity (%)	5/25 (20.0)	0 (−)	0.152	NA	NA
Indications for genetic testing					
Epilepsy (%)	3/30 (10.0)	5/11 (45.4)	**0.022**	NA	NA
Movement disorders (%)	0/30 (−)	6/11 (54.5)	< **0.001**	NA	NA
(Hemiplegic) Migraine (%)	0/30 (−)	1/11 (9.1)	0.286	NA	NA
Developmental problems (%)	26/30 (86.7)	0/11 (−)	< **0.001**	NA	NA
Obesity (%)	3/30 (10.0)	0/11 (−)	0.551	NA	NA
Other (dysmorphisms, behavioral problems, family history) (%)	15/30 (50.0)	2/11 (18.2)	0.085	NA	NA

If patients had missing information, a denominator is given that represents the number of patients with known information on this variable. If no denominator is given, there was information on all patients. P-values in bold were considered significant ($p < 0.05$).
Abbreviations: BIE = benign infantile epilepsy, NA = not available, PKD = paroxysmal kinesigenic dyskinesia, PKD/IC = paroxysmal kinesigenic dyskinesia with infantile convulsions.

[a] p-values of comparisons between patients with a 16p11.2 deletion and patients in our cohort with a *PRRT2* sequence variant. Fisher's exact tests were used for categorical data and Mann-Whitney U tests for continuous variables.

[b] All patients with a heterozygous *PRRT2* sequence variant included in the review study by Ebrahimi et al. (see also methods section).

[c] p-values of comparisons between patients with a 16p11.2 deletion and patients from the review cohort with a *PRRT2* sequence variant. Fisher's exact tests were used for categorical data and Mann-Whitney U tests for continuous variables.

[d] Other epilepsy diagnoses included epilepsy/seizures not otherwise specified, febrile seizures plus, absence seizures, Dravet syndrome, generalized epilepsy with febrile seizures, West syndrome and benign Rolandic epilepsy.

[e] Other movement disorder diagnoses included paroxysmal non-kinesigenic dyskinesia, paroxysmal exercise-induced dyskinesia, episodic ataxia, writer's cramp and paroxysmal torticollis.

[f] Patients with intellectual disability or learning disabilities.

[g] Three females aged 6 years, 21 years† and 29 years were not able to walk or talk.

has thus far been overestimated in patients with a *PRRT2* loss-of-function variant is important for counseling, because increasingly used whole exome sequencing (WES) may detect these variants as secondary findings. Doctors are tempted to use large cohort studies to counsel patients with such unexpected findings, but should realize that ascertainment bias is always present in these studies.

5. Conclusion

We conclude that 16p11.2 deletions including *PRRT2* and *PRRT2* sequence variants both lead to the *PRRT2*-associated phenotypes BIE, PKD or PKD/IC, but with incomplete penetrance. *PRRT2*-related phenotypes were more commonly found in patients with *PRRT2* sequence variants, despite the shared underlying *PRRT2* loss-of-function disease mechanism. Ascertainment bias has led to an overestimation of the penetrance of BIE, PKD and PKD/IC in patients with a *PRRT2* sequence variant. This study is important for the clinical interpretation of *PRRT2* sequence variants found by WES in patients without these specific phenotypes.

6. Web resources

We used the following URLs for data:

Exome Aggregation Consortium (ExAC), http://exac.broadinstitute.org.

Genome Aggregation Database (gnomAD), http://gnomad.broadinstitute.org/

Exome Variant Server (EVS), http://evs.gs.washington.edu/EVS/

Expression Atlas for gene expression, http://www.ebi.ac.uk.

Online Mendelian Inheritance in Man (OMIM), https://www.omim.org.

UCSC Genome Bioinformatics, https://genome.ucsc.edu.

European Cytogeneticists Association Register of Unbalanced Chromosome Aberrations (ECARUCA), http://ecaruca.radboudumc.

Table 2
Epilepsy phenotypes in patients with a 16p11.2 deletion or a *PRRT2* sequence variant.

Pt	Sex, age in years	Epilepsy syndrome diagnosis	PKD	Age at onset of seizures	Age at remission of seizures	Total number of seizures	Seizure type	Anti-epileptic drugs (effect)	EEG at onset of epilepsy	Brain imaging	Developmental problems
16p11.2 deletions (n = 5)											
2	F, 3	BIE	No	4m	12m	10–25	FMS (tonic-clonic)	LEV (+)	Functional disorder left frontotemporal with epileptiform abnormalities?	Wide peripheral cerebrospinal fluid spaces (L > R) on MRI	DD
3	F, 15	BIE	No	4m	4y	> 25	FIAS, FBTCS	VPA (+)	Normal	MRI normal	DD/ID
42	F, 29	BIE	No	5m	7m	1–5	Unknown	Unknown	Unknown	Unknown	Severe DD/ID
1	M, 13	Focal epilepsy	No	12y	No	20/day	FMS (atonic), FIAS	VPA (+)	Unknown	Unknown	DD/ID
33	F, 21 †	Focal epilepsy	No	0m	21y †	10-50/day	UTS, FIAS, FBTCS	VPA (+), LTG (unknown)	Unknown	Unknown	Severe DD/ID
***PRRT2* sequence variants (n = 7)**											
6	M, 4	BFIE	No	5m	6m	5–10	FMS (tonic)	LEV (+)	Not performed	Not performed	No
10	F, 24	BFIE	No	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	No
17	F, 13	BIE	Yes	8m	8m	5	FMS (tonic-clonic)	PHB (+)	Normal	Ultrasound normal	No
35	F, 22	BFIE	Yes	8m	8m	7	FMS (tonic-clonic)	VPA (+)	Normal	MRI normal	No
36	F, 5	BFIE	No	6m	2y	> 25	FBTCS	LEV (−), CBZ (−), LTG (+)	Epileptiform activity left occ., sometimes spreading to right occ.	MRI normal	No
48	F, 48	BFIE	No	Unknown	1y	Unknown	Unknown	Unknown	Unknown	Unknown	No
7	F, 31	Unclassified	No	28y	29y	1–5	UTCS	Unknown	Unknown	Unknown	No

Treatment effect: + treatment response, defined as > 50% seizure frequency reduction, - no treatment response.
Abbreviations: BIE = benign infantile epilepsy, BFIE = benign familial infantile epilepsy, CBZ = carbamazepine, DD = developmental delay, FBTCS = focal to bilateral tonic-clonic seizures, FIAS = focal impaired awareness seizures, FMS = focal motor seizures, ID = intellectual disability, L = left, LEV = levetiracetam, LTG = lamotrigine, occ. = occipital, PHB = phenobarbital, PKD = paroxysmal kinesigenic dyskinesia, R = right, UTCS = unknown onset tonic-clonic seizure, UTS = unknown onset tonic seizure, VPA = valproic acid.

Table 3
Movement disorders in patients with a 16p11.2 deletion or a *PRRT2* sequence variant.

Pt.	Sex, age in years	Movement disorder	BIE	Age at onset	Age at remission	Motor DD	Previous medication (effect)	Current medication [a] (effect)
16p11.2 deletions (n = 1)								
3	F, 15	Myoclonic dystonia with cortical myoclonus	Yes	Birth	No	Yes	VPA (+, but side-effects)	CZP (+)
***PRRT2* sequence variants (n = 8)**								
7	F, 31	PKD	No	9y	No	No	CBZ (+)	None
8	M, 18	PKD	No	14y	16y	No	None	CBZ (+)
17	F, 13	PKD	Yes	10y	12y	No	CZP (−)	CBZ (+)
20	F, 20	PKD	No	8y	19y	No	None	None
35	F, 22	PKD	Yes	14y	14y	No	None	OXC (+)
44	M, 34	PKD	No	8y	No	No	L-DOPA (−), CBZ (+, but side-effects)	None
49	M, 24	PKD	No	10y	No	No	CBZ (+), LEV (−), OXC (side-effects), GBP (−)	LTG (+)
53	F, 18	PKD	No	15y	16y	Yes [b]	None	CBZ (+)

Treatment effect: + treatment response, - no treatment response.
Abbreviations: BIE = benign infantile epilepsy, CBZ = carbamazepine, CZP = clonazepam, DD = developmental delay, GBP = gabapentin, L-DOPA = levodopa, LTG = lamotrigine, OXC = oxcarbazepine, PKD = paroxysmal kinesigenic dyskinesia, VPA = valproic acid.
[a] At last moment of contact with specialist.
[b] Attributed to perinatal asphyxia.

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Leiden Open Variation Database (LOVD), http://www.lovd.nl/PRRT2.

DatabasE of genomiC varIation and Phenotype in Humans using Ensembl Resources (DECIPHER), https://decipher.sanger.ac.uk/

Conflicts of interest

None of the authors have any conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejmg.2018.08.002.

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